A Transcatheter InterAtrial Shunt Device for the Treatment of Heart Failure with Preserved Ejection Fraction (REDUCE LAP-HF I):
A Phase 2, Randomized, Sham-Controlled Trial

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Word count: 4,593

Tables: 4

Figures: 3

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ABSTRACT

Background: In non-randomized, open-label studies, a transcatheter interatrial shunt device (IASD, Corvia Medical) was associated with lower pulmonary capillary wedge pressure (PCWP), less symptoms, and greater quality of life and exercise capacity in patients with heart failure (HF) and mid-range or preserved ejection fraction (EF≥40%). We conducted the first randomized, sham-controlled trial to evaluate the IASD in HF with EF>40%.

Methods: REDUCE LAP-HF I was a phase 2, randomized, parallel-group, blinded multicenter trial in patients with New York Heart Association (NYHA) class III or ambulatory class IV HF, EF ≥ 40%, exercise PCWP ≥ 25 mmHg, and PCWP-right atrial pressure gradient ≥ 5 mmHg. Participants were randomized (1:1) to the IASD vs. a sham procedure (femoral venous access with intracardiac echocardiography but no IASD placement). The participants and investigators assessing the participants during follow-up were blinded to treatment assignment. The primary effectiveness endpoint was exercise PCWP at 1 month. The primary safety endpoint was major adverse cardiac, cerebrovascular, and renal events (MACCRE) at 1 month. PCWP during exercise was compared between treatment groups using a mixed effects repeated measures model analysis of covariance that included data from all available stages of exercise.

Results: A total of 94 patients were enrolled, of which n=44 met inclusion/exclusion criteria and were randomized to the IASD (n=22) and control (n=22) groups. Mean age was 70±9 years and 50% were female. At 1 month, the IASD resulted in a greater reduction in PCWP compared to sham-control (P=0.028 accounting for all stages of exercise). Peak PCWP decreased by 3.5 [SD 6.4] mmHg in the treatment group vs. 0.5 [SD 5.0 mmHg] in the control group (P=0.14). There were no peri-procedural or 1-month MACCRE in the IASD group and 1 event (worsening renal function) in the control group (P=1.0).

Conclusions: In patients with HF and EF≥40%, IASD treatment reduces PCWP during exercise. Whether this mechanistic effect will translate into sustained improvements in symptoms and outcomes requires further evaluation.

Clinical trial registration: URL: http://clinicaltrials.gov. Unique identifier: NCT02600234.

CLINICAL PERSPECTIVE

What Is New?

- We report a novel therapy for patients with heart failure with preserved ejection fraction (HFpEF, EF>50%) or mid-range EF (EF 40-50%) utilizing an implanted device to create an atrial shunt (InterAtrial Shunt Device [IASD]).
- The objective of the IASD is to dynamically (at rest and during exercise) decompress left atrial pressure overload associated with HFpEF and HFmrEF.
- We conducted a randomized, sham-controlled trial to evaluate the mechanistic effect of the IASD on invasively measured pulmonary capillary wedge pressure (PCWP). At 1 month after randomization, the IASD treatment group had a significantly greater reduction in PCWP during exercise compared to the control group. In addition, PCWP during passive leg raise and also during 20W of exercise decreased to a greater degree in the patients randomized to IASD compared to sham-control.

What Are the Clinical Implications?

- In patients with HF with EF≥40% creation of an atrial shunt with the IASD unloads the left atrium and reduces PCWP during exercise.
- This hemodynamic study demonstrates the beneficial mechanistic effect of IASD.
- The IASD could have beneficial clinical effects in patients with HFpEF and HFmrEF. A larger trial to examine the effects of the IASD on symptoms, quality of life, exercise capacity, and clinical outcomes such as HF hospitalization is warranted.

INTRODUCTION

Heart failure (HF) with preserved ejection fraction (HFpEF, EF>50%), which is increasing in prevalence and currently accounts for approximately 50% of all HF cases, is associated with high morbidity and mortality, and lacks effective therapies.[1,2] HF with mid-range EF (EF 40-50%) is also prevalent and lacks proven therapies, and was recently highlighted in the European Society of Cardiology HF guidelines.[3,4] Although HFpEF and HF with mid-range EF are heterogeneous with respect to etiology and pathophysiology, elevated left atrial (LA) pressure at rest and/or during exertion represents a central underlying abnormality in all patients with these syndromes.[5]

Patients with HFpEF are known to have left ventricular (LV) diastolic dysfunction (impaired LV relaxation and reduced LV compliance).[6,7] These abnormalities result in elevated LA pressure and volume overload with subsequent elevation in pulmonary venous pressures, particularly during exertion, resulting in symptoms of dyspnea and exercise intolerance.[8] In addition, intrinsic LA mechanical dysfunction is increasingly recognized as potentially important in driving symptoms and poor outcomes in HFpEF.[5,9-11] The inability of the LA to handle increased load during exercise is especially problematic in HFpEF patients.[5,12] Pulmonary capillary wedge pressure (PCWP) is an invasive hemodynamic parameter that reflects LA and pulmonary venous pressures. Higher peak PCWP during exercise, corrected for workload, has also been associated with reduced exercise capacity[13] and worse outcomes[14] in the setting of HFpEF, further underscoring the importance of the LA in the pathogenesis of HFpEF.

Given the importance of LA overload in HF—particularly HFpEF—unloading the LA with the goal of reducing pulmonary venous pressure may lead to improved symptoms and outcomes in these patients.[15] It has long been known that in the setting of mitral stenosis, a condition also associated with elevated LA pressure and LA dysfunction, the co-existence of a congenital atrial septal defect (Lutembacher syndrome) can be associated with less symptoms and a more favorable clinical course.[16] It has been hypothesized that an interatrial septal communication can unload the LA in the setting of increased LA pressure (such as during exercise), transferring the excess LA blood volume to the larger reservoir of the right atrium (RA) and systemic veins, thereby limiting the increase in LA pressure and pulmonary venous pressures during exercise. The recognition of this concept led to the development of a novel interatrial shunt device (IASD, Corvia Medical) for the treatment of HF.[17]

Hemodynamic simulations of IASD have shown LA unloading during exercise, without right ventricular (RV) pressure or volume overload.[15] In non-randomized, open-label, single-arm studies, placement of the IASD has been associated with lowering of PCWP (a surrogate for LA pressure) during exercise in patients with HF and EF≥40%.[18-20] In these prior studies, the IASD was also found to be safe and associated with fewer symptoms, better quality of life, and greater exercise capacity, without the development of right-sided HF or pulmonary hypertension. However, these were open-label, non-randomized studies that are subject to potential bias and confounding, and cannot prove effectiveness of the IASD. We therefore conducted a randomized, blinded, sham-controlled clinical trial to determine the effectiveness of the IASD in HF with EF≥40%. We hypothesized that the IASD reduces PCWP during exercise in patients with HF and EF≥40% by unloading the LA.

METHODS

Study design and participants

The rationale and design of the REDUCE LAP-HF I trial have been described previously.[17] The primary objective of the REDUCE LAP-HF I clinical trial was to evaluate the mechanistic effect of implanting the IASD System II (Corvia Medical, Tewksbury, Massachusetts, USA) in HF patients with EF≥40% and elevated LA pressure who remained symptomatic despite optimal guideline-directed medical therapy. This was a multi-center, prospective, randomized, controlled, blinded trial, with non-implant (sham) control group and 1:1 randomization. Patients were recruited between February 3, 2016 and November 23, 2016 at 22 centers in the United States, Europe (Belgium, France, Netherlands, and United Kingdom), and Australia.

A full list of inclusion and exclusion criteria are listed in the online-only Data Supplement. The inclusion and exclusion criteria were designed to ensure that patients had symptomatic HF (New York Heart Association [NYHA] class III or ambulatory class IV), an elevated LA pressure with a pressure gradient between the LA and RA, and no evidence of right-sided HF. Key inclusion criteria included documented chronic symptomatic HF and (1) prior hospitalization for HF (or acute care facility/emergency room intensification of diuretic therapy) within the prior 12 months, or (2) elevated B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NTproBNP) within the past 6 months (BNP > 70 pg/mL in normal sinus rhythm, > 200 pg/mL in atrial fibrillation, or NTproBNP > 200 pg/mL in normal sinus rhythm or > 600 pg/mL in atrial fibrillation); EF ≥ 40%; age ≥ 40 years; elevated LA pressure documented invasively by end-expiratory PCWP during supine bike exercise ≥ 25 mmHg, and PCWP-RA pressure (RAP) gradient ≥ 5 mmHg. Key exclusion criteria included stage D HF; cardiac index < 2.0 L/min/m^2; history of stroke, transient ischemic attack, deep vein thrombosis, or pulmonary embolism within the past 6 months; hemodynamically significant valvular disease; hypertrophic or infiltrative cardiomyopathy; RV dysfunction (> mild RV dysfunction, tricuspid annular plane systolic excursion < 1.4 cm, RV size > LV size, or RV fractional area change < 35%); resting RAP > 14 mmHg; or pulmonary vascular resistance > 4 Wood units.

The study protocol was approved by the institutional review board or ethics committee at each of the 22 enrolling sites, and all enrolled patients provided written informed consent. A data safety monitoring committee oversaw the program and reviewed trial data for patient safety at regular intervals. Because of the proprietary nature of the study data, it will not be made publically available at this time. All statistical analyses were performed independently by the Baim Clinical Research Institute.

Randomization and blinding

Eligible patients were randomized if they met all of the inclusion and exclusion criteria after undergoing the study-related qualification procedures (see online-only Data Supplement, Figure S1), including non-invasive screening with echocardiography and supine bicycle exercise right heart catheterization. Immediately following qualification, eligible patients were randomized in a 1:1 ratio to the treatment or control group. Patient randomization was performed via the Interactive Web Response System. Patient blinding included sedation, earphones with music to preclude the patient from hearing the procedural discussions, and blindfolding (or the use of opaque screens) to prevent the participant from viewing the imaging screens. Participants and non-procedural research staff were blinded to treatment assignment for 1 year following randomization. Each site was assigned blinded and unblinded staff to facilitate unbiased patient assessments through follow-up. The physicians managing the randomized patients clinically (including the treating cardiologist) and research staff involved in conducting selected post-randomization evaluations, including the hemodynamic core laboratory, were blinded to study arm. Treating physicians were also blinded to all right heart catheterization measurements. Research staff were given explicit instructions to maintain patient blinding throughout the trial (online-only Data Supplement).

Study procedures

Prior to enrolling patients into the study, all interventional cardiology investigators and associated investigative staff at each site underwent training to optimize and standardize invasive hemodynamic testing and recording of hemodynamic data, and to ensure proper deployment of the IASD System II device.

Once enrolled into the study, all patients underwent non-invasive screening, including comprehensive echocardiography to ensure EF≥40%, diastolic dysfunction, and the absence of significant RV dysfunction or valvular disease. Participants meeting echocardiographic criteria underwent further screening with invasive hemodynamic testing. Right heart and pulmonary arterial catheterization was performed from the right internal jugular vein approach using the standard Seldinger technique under fluoroscopic guidance. Using a fluid-filled pulmonary artery catheter, all participants underwent recording of hemodynamics (RA pressure, pulmonary artery pressure, and PCWP) with a properly zeroed and calibrated pressure transducer. Hemodynamic measurements were recorded at rest, with legs up in the exercise bike pedals [equivalent to a passive leg raise procedure, a preload challenge], and during supine bike exercise. All pressures recordings were performed at a 50 mm/s paper speed with adjustment of pressure (mmHg) scale as needed, and the recordings were saved for blinded measurement by the hemodynamic core laboratory. Cardiac output was measured with the thermodilution method, and pulmonary vascular resistance was calculated as the transpulmonary gradient (mean pulmonary artery pressure – PCWP) divided by cardiac output.

After the baseline right heart catheterization and exercise protocol, all patients who remained eligible by invasive hemodynamic criteria were sedated, blinded using the methods described above, and randomized to IASD treatment or sham control. Both treatment and control arm patients underwent femoral venous access after randomization. Patients randomized to the control arm underwent intracardiac or transesophageal echocardiographic examination of the atrial septum and LA appendage (but no transseptal puncture). Patients randomized to the treatment arm underwent a transseptal puncture and IASD System II implantation guided by fluoroscopy and intracardiac or transesophageal echocardiography. The IASD System II consists of a 1-piece self-expanding metal cage that has a double-disc design with an opening (barrel) in the center (**Figure 1A-C**). The implant is radiopaque and echogenic to allow for imaging during the implantation procedure. The LA side of the implant is flat so the legs rest flush against the LA wall, thereby minimizing the LA profile of the deployed implant. The RA side is curved to accommodate variable interatrial septal wall thicknesses, with only the leg ends contacting the RA wall. The expanded external diameter of each disc is 19.4 mm. The inner diameter of the barrel in the center of the fully expanded implant is 8 mm, which corresponds to the optimal interatrial communication size (i.e., maximizing ability to reduce PCWP during exercise, while keeping the ratio of pulmonary to systemic blood flow at 1.2-1.3; **Figure 1D**).[15] Details regarding medication administration related to the procedure and device are listed in the online-only Data Supplement (**Supplementary Table S1**). Patients randomized to the IASD who were not previously on an anticoagulant (e.g., warfarin, direct oral anticoagulant) were treated with clopidogrel post-procedure. All patients who were on clopidogrel at baseline were kept on clopidogrel post-procedure. All patients in both treatment arms received aspirin post-procedure. The baseline use of these medications (prior to randomization) is listed in **Supplementary Table S2**.

At 1 month after randomization, all study patients underwent repeat right heart catheterization with hemodynamic measurements at rest, with legs up, and during exercise using the exact same protocol as the exercise study performed at baseline. The primary effectiveness endpoint was change in PCWP during exercise from baseline to 1 month. All hemodynamic pressure measurements for the trial were made at end-expiration using a standardized measurement protocol by the hemodynamic core laboratory, which was blinded to treatment allocation, baseline vs. follow-up procedure, and all other clinical data. After initial review, for patients with hemodynamic values that were outside the expected range (e.g., PCWP > mean pulmonary artery pressure) a systematic re-ascertainment of hemodynamic tracings for those patients was conducted by the hemodynamic core laboratory in a blinded fashion as part of their quality assurance process. Secondary effectiveness endpoints included change in peak exercise PCWP from baseline at 1 month, change in exercise duration at 1 month, and change in peak exercise workload at 1 month. Additional endpoints included change in NYHA class and change in diuretic use from baseline.

The primary safety endpoint was peri-procedural events and major adverse cardiac, cerebrovascular, and renal events (MACCRE) at 1 month. MACCRE included cardiovascular death, embolic stroke, device and/or procedure-related adverse cardiac events, new-onset or worsening of kidney dysfunction (defined as a decrease in estimated glomerular filtration rate > 20 mL/min/1.73 m^2) through 1-month post implant. Additional safety-related endpoints included the need for implant removal or occlusion of the implant, and HF hospitalization. All endpoints were adjudicated centrally by a blinded, independent clinical events committee.

Statistical analysis

The statistical analyses for the primary efficacy and safety outcomes (including power calculations and the use of a mixed effects model repeated measures [MMRM, described below]) were pre-specified *a priori* and documented in the trial protocol and in our prior publication on the rationale and design of the REDUCE LAP-HF I trial.[17] We assumed a mean change in exercise PCWP of -6.0 mmHg in the treatment group and 0.0 mmHg in the control group at each of 20W, 40W, 60W and 80W stages, and assumed a standard deviation in PCWP change of 7.2 mmHg in each treatment group at each of the stages of exercise. Based on these assumptions, a sample size of 20 evaluable participants per treatment arm yielded 82% power at a 2-sided 0.05 level of significance to detect a significant beneficial effect of IASD System II over control when comparing treatment means using a mixed effects model repeated measures (MMRM)[21] analysis of covariance (ANCOVA) that included data from all available stages of exercise, assuming the compound symmetry correlation structure where the pairwise correlations between 20W, 40W, 60W and 80W stages of exercise are 0.8 or less.

The key safety outcome analysis on the endpoint of MACCRE at 1 month is descriptive (percentage of patients with MACCRE and two-sided exact confidence interval of the percentage based on the binomial distribution for each treatment group). It was anticipated that the true MACCRE rate in the population would be approximately 5%. Under this assumption, there was a 92% chance in a sample of size of 20 that the observed rate would be 10% or less. This analysis was carried out on the intention-to-treat population (ITT; all randomized participants [n=44], which was identical to the safety population) with available data (follow-up through 1 month, or a MACCRE event by 1 month. Sample size calculations were performed using PASS 14 software (NCSS, LLC, Kaysville, Utah, USA).

The primary analysis was based on an ITT analysis that included all randomized patients with available data (n=44; n=22 in each treatment arm). Femoral venous access was attempted on all ITT patients; thus, the safety population (n=44) was identical to the ITT population. The per-protocol population consisted of 42 patients (2 of the patient randomized to the treatment arm were excluded from the per-protocol population because they did not receive the IASD implant). All statistical tests were carried out at a 2-sided 0.05 level of significance, and all p-values were presented as 2-sided p-values. There was no imputation for missing data. For the primary mechanistic endpoint (change in PCWP during exercise from baseline at 1 month), the 2 treatment groups were compared using the aforementioned pre-specified MMRM ANCOVA, which included data from all available stages of exercise. For the primary safety endpoint (peri-procedural and 1-month MACCRE), the 2 treatment groups were compared using a 2-sided exact confidence interval of the percentage of patients who experienced events in the 2 groups based on the binomial distribution for each treatment arm; given the sample size and low MACCRE rates that were expected, there was no anticipation of a treatment difference on 1-month MACCRE. Mean values of continuous secondary effectiveness outcomes were compared between treatment groups using ANCOVA with adjustment for the baseline value of the variable of interest. The rate of HF hospitalization was compared between treatments using the Fisher exact test. Mean differences between baseline and 1-month PCWP at rest (legs down), legs up, 20W, and peak exercise were calculated using paired t-tests within each treatment group. Analyses were carried out using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

This trial is registered at ClinicalTrials.gov, NCT02600234.

Role of the funding source

REDUCE LAP-HF I was designed jointly by the academic steering committee and the sponsor. The study was funded by Corvia Medical Inc. Data collection and analyses were done by the Baim Clinical Research Institute (Boston, Massachusetts, USA). Interpretation of the results and preparation of the report was the responsibility of the co-principal investigators (TF and SJS) and the chair of the steering committee (LM). Corvia had no role in the collection, analysis, interpretation of data, or the decision to submit for publication. All study authors contributed to data collection and analysis, reviewed the report, read and approved the final version, and endorsed its submission for publication.

RESULTS

A total of 94 patients with HF and EF≥40% underwent screening procedures. Of the 94 enrolled patients, 44 met inclusion/exclusion criteria and were randomized 1:1 to the IASD and control (sham) groups (**Figure 2**). Baseline demographic, clinical, and invasive hemodynamic characteristics were similar between treatment groups except for more black patients in the control arm (**Table 1**). Echocardiographic indices of diastolic function were similar between the treatment groups (**Supplementary Table S3**).

The study participants ranged in age from 48-84 years (mean age 70 years), were 50% women, and had multiple comorbidities (including a 50% prevalence of atrial fibrillation). At the time of screening, all but 1 participant were NYHA class III. The vast majority (42/44, 95%) were on a diuretic at baseline, and 28/44 (64%) of the participants had at least 1 hospitalization or emergency department/acute care facility visit for heart failure HF within the 12 months prior to enrollment. All study participants had an EF ≥ 40% at baseline, and the majority (39/44, 89%) had a baseline EF ≥ 50%.

Implantation of the IASD System II was attempted in 21 of 22 of the participants randomized to the treatment arm. In one participant, RA access could not be established for insertion of the procedure catheters (an occluded inferior vena cava filter was noted); therefore, the procedure was aborted. No subsequent MACCRE events were reported in this participant. Of the 21 remaining participants in whom implantation was attempted, there was one participant in whom the device was inadvertently fully deployed in the LA instead of at the interatrial septum. The device was percutaneously retrieved over the guidewire and the implantation of a second device was not attempted (see online-only Data Supplement for further details [**Supplementary Table S4**]). The 20 remaining participants randomized to the IASD treatment arm were successfully implanted; 19 participants had one implantation attempt and one participant had two implantation attempts. **Table 2** lists the differences in procedure characteristics between study groups. Total procedure duration, total fluoroscopy duration, and total contrast administered were greater in the treatment group compared to the control group. See online-only Data Supplement (**Supplementary Table S4**) for further details about the procedural and device characteristics. Of the 20 participants who underwent successful device implantation, one refused repeat right heart catheterization at 1 month but remained in the trial and underwent all other follow-up assessments. All 22 control arm patients underwent repeat right heart catheterization with invasive hemodynamic testing at 1 month.

The ITT analysis of the key effectiveness endpoint (PCWP during exercise) was performed on all participants who had PCWP results for at least one exercise level (at 20W, 40W, 60W or 80W) at both baseline and 1 month (all participants achieved an exercise level of at least 20W at 1 month). These results are shown in **Table 3**. Overall, the IASD treatment group had a greater reduction in PCWP during exercise after 1 month compared to the control group ($p=0.028$ by MMRM ANCOVA). Thus, the trial met its key effectiveness endpoint measure. On secondary outcome analysis, the change in peak PCWP at 1 month was -3.5±6.4 mmHg in the treatment group compared to -0.5±5.0 mmHg in the control group ($P=0.14$). As shown in **Figure 3**, patients randomized to the IASD arm had a reduction in 1-month PCWP at legs up, 20W, and peak exercise ($P<0.05$ for all comparisons) while the control group did not. From baseline to 1 month, the exercise time increased by a mean of 1.2±3.7 minutes in the treatment group compared to 0.4±3.5 minutes in the control group ($P=0.60$); and peak supine bike workload increased by a mean of 1.5±14.6 Watts in the treatment group compared to -1.9±10.8 Watts in the control group ($P=0.35$). On exploratory analyses, legs up PCWP and 20W PCWP decreased to a greater amount in the IASD treatment group compared to the control group ($P<0.05$ for both comparisons) (**Table 3**). Results of the per-protocol analyses were very similar to the results of the ITT analysis described above.

Overall, there were very few peri-procedural, MACCRE, or other serious adverse events in either the treatment or control groups at 1 month of follow-up (**Table 4**). At 1 month, 0/21 (0%) of the participants in the treatment group experienced a MACCRE event and 1/22 (4.5%) of the participants in the control group experienced a MACCRE event (new onset/worsening kidney function event), $P=1.0$. At 1 month of follow-up there were no deaths; myocardial infarctions; post-procedural IASD occlusions or removals; or strokes or transient ischemic attacks reported in either of the study arms. Furthermore, during the 1-month follow-up period, none of the study participants in normal sinus rhythm at baseline developed new-onset atrial fibrillation or flutter, and there were no systemic embolic events or cardiac perforation, cardiac tamponade, or emergency cardiac surgery reported in either of the study arms.

At 1 month of follow-up, the rate of HF-related hospitalizations or emergency department/acute care facility visits requiring intravenous treatment was 0/21 (0.0%) in the treatment arm compared to 2/22 (9.1%) in the control arm (P=0.49). There were no significant differences in loop diuretic dose (furosemide equivalents, in mg) at baseline or at 1 month of follow-up between the 2 treatment groups (mean change from baseline of -0.9±9.7 mg in the treatment group vs. 0.9±20.0 mg in the control group, P=0.70).

DISCUSSION

The REDUCE LAP-HF I randomized, blinded, sham-controlled trial was designed to test the hypothesis that the implantation of the IASD System II device in the interatrial septum in patients with symptomatic HF and mid-range or preserved EF (≥40%) results in lowering of PCWP during exercise. The trial met its primary effectiveness endpoint, with statistically significant lowering of PCWP during exercise at 1 month of follow-up (p=0.028). The 3-mmHg reduction in peak exercise PCWP in the IASD arm at 1 month is similar to the reduction seen in the prior observational study (n=64, all of whom received the IASD) at 6 months.[18,19] Although the decrease in peak exercise PCWP is modest, it was associated with clinically important improvements in exercise duration and quality of life in the prior observational study, which were observed at both 6 and 12 months after IASD implantation.[18,19]

The REDUCE LAP-HF I trial also showed that the IASD device was safe at 1 month. In 1 patient the IASD was mal-deployed in the left atrium, but since the device remains on the guidewire after deployment and is fully retrievable, it was safely removed. The key safety outcome measure for the trial was MACCRE at 1 month, defined as the composite of cardiovascular death, embolic stroke, device and/or procedure related adverse cardiac events, and new-onset or worsening kidney dysfunction. Implantation of the IASD appeared to be safe at 1 month, with no MACCRE events reported in the IASD treatment arm compared to a 1-month MACCRE rate of 4.5% in the control arm. In addition, no patients in the treatment arm developed post-procedural persistent or permanent atrial fibrillation/flutter or complications such as cardiac perforation, cardiac tamponade, emergency cardiac surgery, systemic embolization, or major vascular complications. Finally, consistent with prior observational trials of the IASD, none of the treatment arm patients experienced device embolization, device occlusion, or device migration, and none of them required a repeat procedure for removal or occlusion of the device.

As shown in **Table 1**, the patients enrolled in the trial were similar to those in prior studies of patients with HFpEF.[22] Participants were elderly, 50% female, and were obese and had multiple comorbidities. Left ventricular EF was preserved (>50%) in the majority, and most of the participants were on a relatively high dose of diuretics and had a prior HF hospitalization or acute care visit within the last 12 months. On invasive hemodynamic testing, baseline resting PCWP was elevated (mean 20 mmHg) despite being on a mean dose of diuretics of 103 mg furosemide-equivalents per day. Thus, the patients were symptomatic and had significant HF. Patients enrolled in REDUCE LAP-HF I were generally similar to those enrolled in HFpEF epidemiologic studies[23] and also contemporary HFpEF clinical trials.[22] However, unlike these prior studies, patients enrolled in the present trial had objective evidence of elevated LV filling pressure (i.e., PCWP) at rest and during exercise at baseline, which confirmed the HF diagnosis. Together, these findings show that patients enrolled in REDUCE LAP-HF I represented contemporary HFpEF patients encountered in clinical practice.

The findings from REDUCE LAP-HF I trial are important because they are the first randomized data for this device. In the prior observational, open-label studies of the Corvia IASD in patients with HFpEF, including a total of 75 patients with the IASD implanted,[18-20] the IASD was associated with lower PCWP during exercise, greater exercise capacity, and an excellent safety profile, but none of these prior studies were conclusive because they were non-randomized and therefore subject to potential bias and confounding. In the present trial, randomized evaluation of the IASD confirmed the lowering of PCWP during exercise and demonstrated improvements in workload-corrected PCWP, exercise duration, and peak exercise workload compared to sham control. However, while these latter secondary outcomes were numerically better in the treatment group, the differences did not achieve statistical significance, as the trial was not powered to demonstrate effectiveness in these endpoints.

Despite the fact that patients with HFpEF have evidence of pulmonary vascular stiffening, in open-label treated HFpEF patients enrolled in prior studies,[19] left-to-right shunting through the IASD (which increases flow through the pulmonary vasculature) was not associated with increased pulmonary artery pressure or pulmonary vascular resistance, both of which could be deleterious in HFpEF due to increased RV load, with subsequent right-sided HF. The present randomized trial findings were similar to the prior open-label studies; there was a greater reduction in mean pulmonary artery pressure and pulmonary vascular resistance in the IASD treatment arm compared to control arm, though these differences did not achieve statistical significance (**Table 3**). Possible explanations for the seemingly paradoxical trend towards lower PA pressures after IASD placement are two-fold. First, elevated PCWP can result in an augmentation of the reflected pressure wave in the pulmonary artery, which would raise pulmonary artery pressures and can lead to increased pulmonary vascular resistance.[24] Lowering of LA pressure and PCWP would therefore tend to reduce the reflected pressure wave, thereby lowering pulmonary artery pressure. Second, the LA blood that is shunted across the IASD is oxygenated and thus increases pulmonary artery saturation. The higher oxygen content in the pulmonary arterial vasculature, which was also seen in response to the IASD in prior non-randomized studies, could have a vasodilatory effect that allows for the ability of the pulmonary vasculature to handle increased flow from the IASD-induced left-to-right shunting. This may be especially evident during exercise, as was seen in the present study (**Table 3**).

Elevated LV filling pressure (i.e., increased PCWP) at rest or during exercise is an important determinant of both symptoms and outcomes in HF patients.[25] Borlaug and colleagues showed that elevated PCWP during exercise can distinguish patients with HFpEF from those with non-cardiac dyspnea, and that the rise in PCWP during exercise is an important pathophysiologic determinant of HFpEF early in the course of the clinical syndrome.[26] PCWP during exercise also correlates with 6-minute walk test distance and is an important determinant of mortality in patients with HFpEF.[13,14] In addition, implantable hemodynamic sensor-guided lowering of pulmonary artery diastolic pressure (a surrogate for PCWP in left heart failure) has been shown to reduce HF hospitalizations in patients with HF and EF > 40%.[27] On this background and in view of the hemodynamic effect of reduced exercise PCWP with the IASD,[18,19] it is expected that treatment with the IASD will result in improved clinical outcomes in HFpEF patients. However, this hypothesis must be tested in a larger, adequately powered randomized controlled trial.

The importance of testing cardiovascular device therapies against sham control procedures cannot be underestimated. The mere act of having an invasive control procedure alone may result in improved symptoms in HF patients. While studies of invasive treatments can be difficult to study in a blinded fashion, lack of blinding may overestimate the effectiveness of treatments.[28,29] Thus, the present trial—which evaluated a hemodynamic primary endpoint in a blinded fashion—is an important step in the development of the IASD as a potential treatment for HF patients. The finding that the IASD does indeed lower exercise PCWP provides a mechanistic rationale for further randomized evaluation of the device in a larger pivotal trial that has clinical endpoints.

Certain limitations should be considered. Although an *a priori* power calculation was conducted showing adequate statistical power with a sample size of n=20 in each treatment group, the overall size of the trial is small. Thus, while the treatment groups were overall well-balanced, there were some demographic and clinical differences between the groups, though only the difference in race/ethnicity was statistically significant. Furthermore, the primary effectiveness endpoint (PCWP during exercise) can be challenging to measure, even with training of sites and the use of a central hemodynamic core laboratory, as was done in the present study. However, the passive preload increase maneuver (which was done in this trial with legs up in the supine exercise bicycle pedals) does not suffer from the motion artifact of exercise but still provides information on how the LA handles an increased load. In the present trial, PCWP during the legs up maneuver decreased significantly at 1 month in the IASD treatment group but not in the control group (**Table 3** and **Figure 3**), supporting the mechanistic effect of the IASD. An additional limitation relates to the use of anticoagulants (i.e., clopidogrel) in the IASD-treated patients not previously on a non-aspirin anticoagulant, but not in sham-control patients. Although we had specific instructions to maintain blinding throughout the trial (see the online-only Data Supplement), we did not administer a questionnaire to evaluate the success of blinding at 1 month (we do have a questionnaire at the 1 year follow-up visit that will evaluate blinding). A final limitation relates to the relatively short time frame of the study (1 month follow-up). However, the open-label studies show prolonged hemodynamic and symptomatic benefits of the IASD at 1 year.[19]

In summary, we found that in patients with HF and EF ≥ 40%, implantation of an IASD reduced PCWP during exercise to a greater extent than a sham control procedure, demonstrating that in HF patients with elevated LA pressure during exercise, the creation of an 8-mm interatrial communication unloads the LA. We also found that the IASD is safe compared to sham control procedure at 1 month, and showed favorable but non-significant trends in several additional secondary hemodynamic and functional endpoints. These findings suggest that the IASD could have beneficial effects in patients with HFpEF and HF with mid-range EF, setting the stage for a larger-scale randomized clinical trial powered to examine the effects of the IASD on symptoms, quality of life, exercise capacity, and clinical outcomes.

CONTRIBUTORS

SJS drafted the report, and all authors participated in editing the report. TF, LM, JM, DB, and SJS participated in the study concept and design, study operations, and data analysis. RK, SL, MR, PvdH, MP, PSF, DMK, MCP, AB, SLH, RFM, CN, SL, and SJS contributed to data collection. All authors read and approved the submission of the final draft of the report.

CONFLICTS OF INTEREST

TF has received consulting fees from Abbott, BSC, Edwards and Gore. LM has received research support from Corvia Medical, Inc. MCP has received speaker fees or consulting honoraria from Takeda, Novartis, AstraZeneca, Maquet, Boehringer Ingelheim, Pfizer, Daiichi-Sankyo, Servier, Eli Lilly, Novo Nordisk; and has served on clinical events committees for Roche, Bayer, Stealth Biotherapeutics, AstraZeneca, GlaxoSmithKline, Astellas, Cardiorentis, Reservlogix, and Boehringer Ingelheim. DB received financial support from Corvia Medical to run the hemodynamic core laboratory and has received consulting fees from Medtronic, Sensible Medical, BackBeat Medical, Impulse Dynamics, Abbott, and Boston Scientific. SJS has received research grants from Actelion, AstraZeneca, Corvia, and Novartis; and consulting fees from Actelion, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Cardiora, Eisai, Ironwood, Merck, Novartis, Sanofi, and United Therapeutics.

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FIGURE LEGENDS

Figure 1.

Title: InterAtrial Shunt Device

Caption: (A) Corvia InterAtrial Shunt Device (IASD) System II; (B) En face view of the IASD System II (single size, internal diameter = 8 mm); (C) The IASD creates an interatrial shunt that unloads the left atrium by shunting blood from the higher pressure left atrium to the lower pressure right atrium; (D) Simulation studies have shown that an 8-mm internal diameter for the shunt device is optimal in maximally reducing left atrial pressure without overloading the right heart (i.e., keeping pulmonary-to-systemic flow relatively low at a 1.2-1.3 range). Figure 1D was reproduced with permission from Kaye D, et al. *J Card Fail* 2014. CVP = central venous pressure (= right atrial pressure); IASD = InterAtrial Shunt Device.

Figure 2.

Title: Study Participant Disposition Flow Chart

Caption: *Reasons for exclusion included myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting within the last 3 months (n=13), known clinically significant unrevascularized epicardial coronary artery disease (n=11), history of stroke, transient ischemic attack, deep vein thrombosis, or pulmonary embolism within the last 6 months (n=5), resting right atrial pressure > 14 mmHg on invasive hemodynamic testing (n=5), not an appropriate participant in the opinion of the investigator (n=5), significant valvular disease (n=4), severe chronic kidney disease (n=2), severe heart failure (n=1), baseline 6-minute walk test outside of acceptable range of 60-500 m, untreated clinically significant carotid stenosis (n=1), right ventricular dysfunction (n=1), significant lung disease (n=1), severe untreated obstructive sleep apnea (n=1), and current immunosuppressive therapy (n=1). In addition, 2 participants could not be enrolled because the study was closed to enrollment during the screening period, and 1 patient was diagnosed with breast cancer and wanted to defer the study while she underwent chemotherapy. Note: some participants had more than 1 reason for being excluded from the trial.

** One participant withdrew consent to participate in the study during the index procedure. Right atrial access could not be obtained for insertion of the intracardiac echocardiography probe and the participant was unblinded immediately after the attempt. The participant withdrew consent at that point upon learning that device placement was not feasible.

Figure 3.

Title: Pulmonary Capillary Wedge Pressure during Exercise Hemodynamic Testing: Baseline vs. 1 Month Post-Randomization, Stratified by Treatment Group

Caption: (A) Control group; (B) IASD treatment group. PCWP = pulmonary capillary wedge pressure. P-values were calculated using paired t-tests (within-group comparisons of baseline vs. 1-month values). Note: between-group comparison of peak exercise PCWP was not statistically significant (P=0.144), as shown in Table 3. *P<0.05; **P<0.01.

TABLES

Table 1. Baseline Demographic, Clinical, and Invasive Hemodynamic Characteristics of the Treatment Groups

Patient Characteristics	IASD (N=22 Patients)	Control (N=22 Patients)	P-value
Demographics			
Age (years)	69.6±8.3 (22)	70.0±9.2 (22)	0.86
Male	63.6% (14/22)	36.4% (8/22)	0.13
Race			0.03
Black	0.0% (0/22)	18.2% (4/22)	
White	86.4% (19/22)	81.8% (18/22)	
Other	13.6% (3/22)	0.0% (0/22)	
Body mass index (kg/m^2)	35.2±6.4 (22)	35.1±9.1 (22)	0.98
Comorbidities/risk factors			
Hypertension	81.8% (18/22)	90.9% (20/22)	0.66
Hyperlipidemia	72.7% (16/22)	72.7% (16/22)	1.00
Diabetes	54.5% (12/22)	54.5% (12/22)	1.00
Chronic obstructive pulmonary disease	13.6% (3/22)	31.8% (7/22)	0.28
Ischemic heart disease	22.7% (5/22)	23.8% (5/21)	1.00
Prior myocardial infarction	22.7% (5/22)	19.0% (4/21)	1.00
Prior coronary revascularization	47.6% (10/21)	45.5% (10/22)	1.00
Atrial fibrillation	54.5% (12/22)	45.5% (10/22)	0.76
Atrial flutter	4.5% (1/22)	9.1% (2/22)	1.00
Stroke	9.1% (2/22)	14.3% (3/21)	0.66
Transient ischemic attack	13.6% (3/22)	9.1% (2/22)	1.00
Peripheral arterial disease	13.6% (3/22)	9.1% (2/22)	1.00
Pulmonary embolism	4.5% (1/22)	4.5% (1/22)	1.00
Deep vein thrombosis	13.6% (3/22)	0.0% (0/21)	0.23
Cardiac Status			
LVEF (site-reported) (%)	59.9±9.0 (22)	58.5±6.9 (22)	0.59
NYHA classification			0.32
III	100.0% (22/22)	95.5% (21/22)	
IV	0.0% (0/22)	4.5% (1/22)	
Loop diuretic dose (mg furosemide equivalents)	92.7±99.4 (22)	113.2±90.3 (22)	
Hospitalization/ER visit/acute care facility visit for HF in the past 12 months	54.5% (12/22)	72.7% (16/22)	0.35
Systolic blood pressure (mmHg)	131±17 (22)	128±22 (22)	0.72
Diastolic blood pressure (mmHg)	68±9 (22)	71±14 (22)	0.53
Mean arterial pressure (mmHg)	89±11 (22)	90±15 (22)	0.84
HR at rest (bpm)	65±7 (22)	72±13 (22)	0.05
HR at peak exercise (bpm)	102±20 (22)	104±21 (22)	0.78
Increase in HR during exercise (bpm)	37±21 (22)	32±25 (22)	0.47
RA pressure (mmHg)	10.1±2.3 (22)	9.1±3.7 (22)	0.27
Mean PA pressure (mmHg)	30.2±9.5 (22)	28.4±8.6 (22)	0.52
Cardiac output (L/min/m)	5.4±1.6 (22)	5.7±2.7 (22)	0.66
Pulmonary vascular resistance (WU)	2.19±1.52 (22)	1.74±1.45 (21)	0.32
PCWP, legs down (mmHg)	20.9±7.9 (21)	19.9±7.5 (22)	0.67
PCWP, legs up (mmHg)	26.6±7.1 (21)	24.0±9.3 (22)	0.32
PCWP, peak exercise (mmHg)	37.3±6.5 (19)	37.3±6.7 (19)	1.00

Patient Characteristics	IASD (N=22 Patients)	Control (N=22 Patients)	P-value
PCWP-RAP gradient at rest (mmHg)	10.8±5.6 (21)	10.9±7.3 (22)	0.95
Workload-corrected PCWP (mmHg/W/kg)	95.0±49.8 (18)	94.1±45.3 (19)	0.74
Exercise duration (minutes)	7.4±3.1 (22)	8.9±4.0 (22)	0.18
Peak exercise workload (W)	42.3±19.5 (22)	41.8±16.2 (22)	0.93

Values in Table 1 represent mean±SD (N) or % (n/N). IASD = InterAtrial Shunt Device; NYHA = New York Heart Association; ER = emergency room; HF = heart failure; RA = right atrial; PA = pulmonary artery; WU = Wood units; PCWP = pulmonary capillary pressure; RAP = right atrial pressure; W = Watts.

Table 2. Procedural and Device Characteristics

Procedure/Device Characteristic	IASD (N=22 Patients)	Control (N=22 Patients)	P-Value
Device implantation attempted (number of patients)	95.5% (21/22)	N/A	--
Total procedure duration (minutes)	58.1±25.8	12.9±9.0	<0.001
Total fluoroscopy time (minutes)	23.3±13.0	5.3±3.6	<0.001
Total contrast agent administered (mL)	19.2±17.4	19.0±15.6	0.986
Femoral venous access*			<0.001
Left only	0.0% (0/22)	4.8% (1/21)	
Right only	18.2% (4/22)	81.0% (17/21)	
Both	81.8% (18/22)	14.3% (3/21)	
Echocardiographic guidance tool used*			0.317
Intra-cardiac echocardiography	95.2% (20/21)	100.0% (21/21)	
Transesophageal echocardiography	4.8% (1/21)	0.0% (0/21)	
Device deficiency**	4.5% (1/22)	N/A	--
Device malfunction***	4.5% (1/22)	N/A	--
Device failure	0.0% (0/22)	N/A	--
Device mal-deployment without embolization****	4.5% (1/22)	N/A	--
L→R flow observed through device barrel	100.0% (20/20)	N/A	--
R→L flow observed through device barrel	15.0% (3/20)	N/A	--

*In 1 patient in the control arm, femoral venous access was attempted but could not be established. Thus, the denominator is n=21 for the control arm for both femoral venous access and echocardiographic guidance tool.
**The device did not deploy properly in 1 patient enrolled in the treatment arm (the left atrium legs of the device did not deploy so the device was removed without incident and another device was successfully deployed).
***In 1 patient enrolled in the treatment arm, a small thrombus was observed on the tip of the device delivery system in the right atrium. The delivery system was removed and exchanged. A new system was then re-inserted and the IASD device was successfully implanted.
****In 1 patient enrolled in the treatment arm, the device was inadvertently mal-deployed in the left atrium. The device remained on the guidewire and was percutaneously removed, and the procedure was subsequently aborted.

Table 3. Key Effectiveness and Safety Outcome Measures

Outcome at 1 month	IASD (N=22 Patients)	Control (N=22 Patients)	P-value
Primary effectiveness outcome (change from baseline to 1 month)			0.028*
PCWP at a workload of 20W (mmHg)**	-3.2±5.2 (n=14)	0.9±5.1 (n=18)	
PCWP at a workload of 40W (mmHg)**	-1.0±4.5 (n=10)	-1.9±4.3 (n=10)	
PCWP at a workload of 60W (mmHg)**	-2.3±4.9 (n=6)	-1.3±4.9 (n=6)	
Primary safety outcome (MACCRE)			1.000
Frequency (n, %)	0/22 (0%)	1/22 (4.5%)	
95% confidence interval	[0.0%, 16.1%]	[0.1%, 22.8%]	
Secondary outcomes (change from baseline to 1 month)*			
Hemodynamic measures			
PCWP, legs down at rest (mmHg)	-2.2±6.6 (n=18)	-0.5±5.0 (n=21)	0.441
PCWP, legs up at rest (mmHg)	-5.0±5.7 (n=19)	0.0±6.4 (n=21)	0.024
PCWP, peak (mmHg)	-3.5±6.4 (n=17)	-0.5±5.0 (n=17)	0.144
PCWP, workload-corrected (mmHg/W/kg)	-5.7±27.3 (n=16)	10.3±45.9 (n=17)	0.231
Right atrial pressure at rest (mmHg)	0.5±4.0 (n=20)	0.5±3.3 (n=20)	0.673
Mean PA pressure at rest (mmHg)	-2.7±5.4 (n=20)	-0.7±4.6 (n=21)	0.111
Cardiac output at rest (L/min)****	1.6±1.3 (n=20)	-0.5±1.4 (n=22)	<0.001
PVR at rest (Wood units)	-0.76±1.59 (n=20)	0.17±1.57 (n=21)	0.102
PVR during exercise (Wood units)	-0.29±1.22 (n=19)	0.31±1.64 (n=21)	0.051
Systolic BP at rest (mmHg)	3.8±22.2 (n=20)	6.2±31.6 (n=22)	0.901
Diastolic BP at rest (mmHg)	1.2±11.4 (n=20)	1.6±21.7 (n=22)	0.592
Mean arterial pressure at rest (mmHg)	2.0±14.0 (n=20)	3.2±23.5 (n=22)	0.725
Heart rate at rest (bpm)	3.2±10.1 (n=19)	0.6±12.3 (n=22)	0.972
Heart rate at peak exercise (bpm)	-2.1±17.6 (n=19)	-3.5±24.0 (n=21)	0.956
Heart rate increase with exercise (bpm)	-5.3±19.4 (n=19)	-3.3±24.0 (n=21)	0.880
Functional capacity			
NYHA class	-0.5±0.7 (n=21)	-0.4±0.7 (n=21)	0.538
Exercise duration (minutes)	1.2±3.7 (n=20)	0.4±3.5 (n=20)	0.603
Peak exercise workload (Watts)	1.5±14.6 (n=20)	-1.9±10.8 (n=21)	0.348
Weight (kg)	-0.56±3.20 (n=21)	-0.25±2.33 (n=22)	0.710

Values represent mean±SD for continuous variables and n/N (%) for categorical variables.
*The p-value for change in supine exercise PCWP from baseline to 1 month was computed using MMRM ANCOVA adjusting for the corresponding baseline values of supine exercise PCWP.
**p=0.019 at 20W, p=0.990 at 40W, and p=0.822 at 60W; p-values calculated using ANCOVA with adjustment for baseline value
***P-values in this section were calculated using ANCOVA with adjustment for baseline value
****Right-sided cardiac output, calculated by the thermodilution method

IASD: InterAtrial Shunt Device; ANCOVA: analysis of covariance; CI: confidence interval; MACCRE: major adverse cardiac, cerebrovascular embolic, or renal events; MMRM: mixed effects model repeated measures; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; BP: blood pressure; NYHA: New York Heart Association

Table 4. Adverse Events (Peri-procedural to 1 month post-randomization)

Adverse event	IASD (N=22 Patients)	Control (N=22 Patients)	P-Value
MACCRE	0.00% (0/21)	4.55% (1/22)	1.000
Cardiovascular Death	0.00% (0/21)	0.00% (0/22)	--
Embolic Stroke	0.00% (0/21)	0.00% (0/22)	--
Device/Procedure Related MACE*	0.00% (0/21)	0.00% (0/22)	--
New Onset or Worsening Renal Dysfunction	0.00% (0/21)	4.55% (1/22)	1.000
MACE	0.00% (0/21)	0.00% (0/22)	--
Cardiac Death	0.00% (0/21)	0.00% (0/22)	--
Myocardial Infarction	0.00% (0/21)	0.00% (0/22)	--
Emergency Cardiac Surgery	0.00% (0/21)	0.00% (0/22)	--
Cardiac Tamponade	0.00% (0/21)	0.00% (0/22)	--
Death	0.00% (0/21)	0.00% (0/22)	--
Myocardial Infarction	0.00% (0/21)	0.00% (0/22)	--
Stroke or TIA	0.00% (0/21)	0.00% (0/22)	--
Systemic Embolization	0.00% (0/21)	0.00% (0/22)	--
Cardiac Perforation	0.00% (0/21)	0.00% (0/22)	--
Newly Acquired Atrial Fibrillation/Flutter	0.00% (0/21)	0.00% (0/22)	--
Major Vascular Complications	0.00% (0/21)	0.00% (0/22)	--
Device Embolization	0.00% (0/21)	0.00% (0/22)	--
Device Occlusion	0.00% (0/21)	0.00% (0/22)	--
Device Related Repeat Procedure	0.00% (0/21)	0.00% (0/22)	--
Heart Failure Event	4.76% (1/21)	13.64% (3/22)	0.607
Heart Failure Event Requiring IV Treatment	0.00% (0/21)	9.09% (2/22)	0.488
Cardiogenic Shock	0.00% (0/21)	0.00% (0/22)	--

Values represent % (n/N)
IASD = InterAtrial Shunt Device; MACCRE = major adverse cardiac, cerebrovascular and renal events; MACE = major adverse cardiac event;
TIA = transient ischemic attack; IV = intravenous
Events in this table have been adjudicated by the independent, blinded Clinical Events Committee..
Denominators indicate the number of patients with at least 23 days of follow-up or an out-of-hospital event through 1 month
*Includes MACE events that were determined by the Clinical Events Committee to be definitely, probably, or possibly related to the procedure and/or device.

FIGURES

Figure 1. InterAtrial Shunt Device

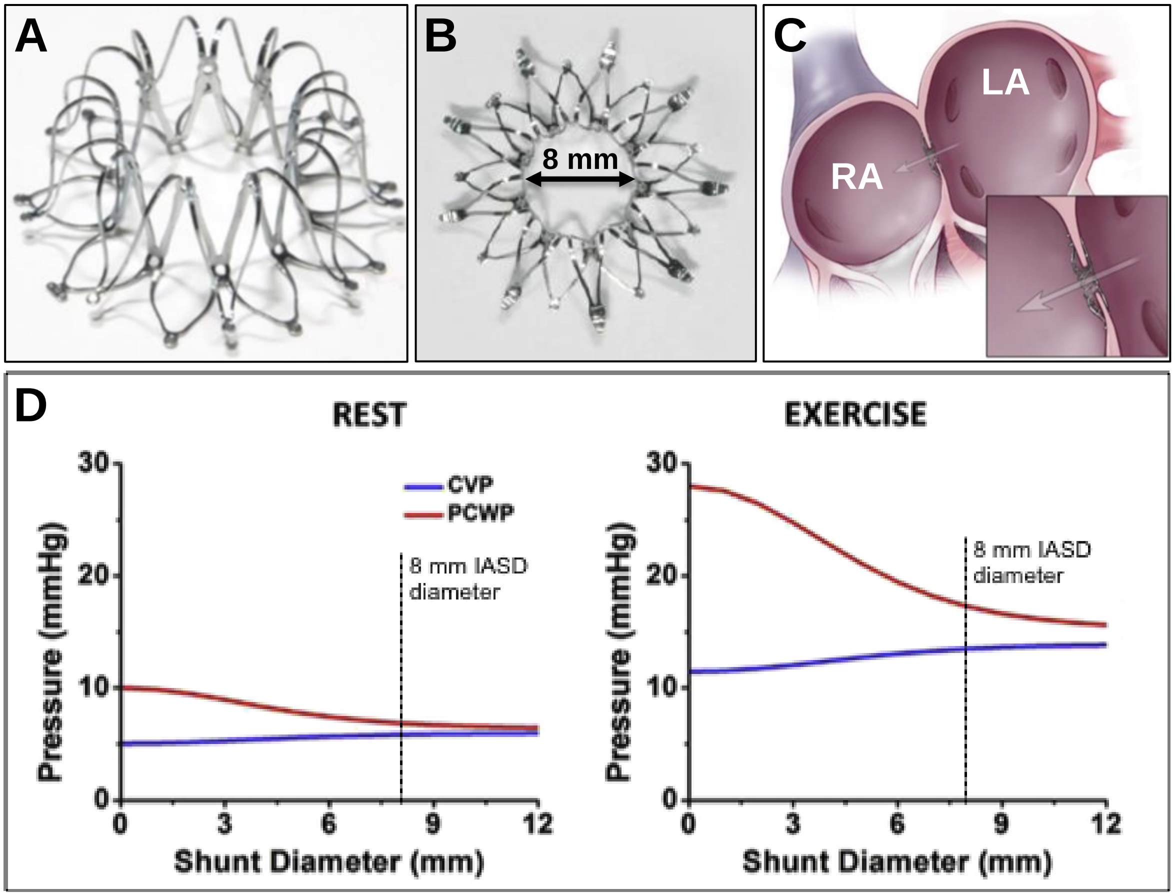
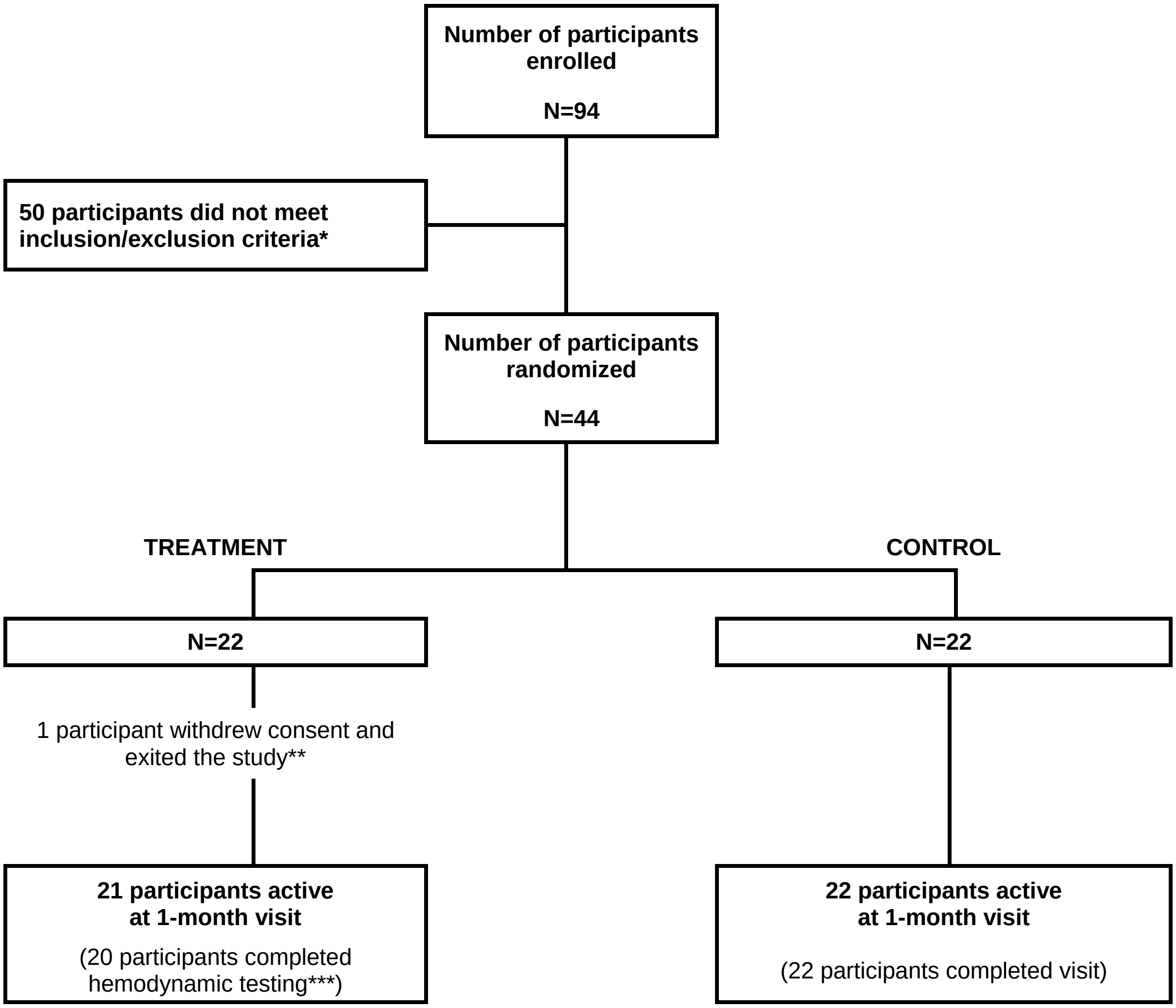


Figure 2. Study Participant Disposition Flow Chart



* Reasons for exclusion included myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting within the last 3 months (n=13), known clinically significant unrevascularized epicardial coronary artery disease (n=11), history of stroke, transient ischemic attack, deep vein thrombosis, or pulmonary embolism within the last 6 months (n=5), resting right atrial pressure > 14 mmHg on invasive hemodynamic testing (n=5), not an appropriate participant in the opinion of the investigator (n=5), significant valvular disease (n=4), severe chronic kidney disease (n=2), severe heart failure (n=1), baseline 6-minute walk test outside of acceptable range of 60-500 m, untreated clinically significant carotid stenosis (n=1), right ventricular dysfunction (n=1), significant lung disease (n=1), severe untreated obstructive sleep apnea (n=1), and current immunosuppressive therapy (n=1). In addition, 2 participants could not be enrolled because the study was closed to enrollment during the screening period, and 1 patient was diagnosed with breast cancer and wanted to defer the study while she underwent chemotherapy. Note: some participants had more than 1 reason for being excluded from the trial.

** One participant withdrew consent to participate in the study during the index procedure. Right atrial access could not be obtained for insertion of the intracardiac echocardiography probe and the participant was unblinded immediately after the attempt. The participant withdrew consent at that point upon learning that device placement was not feasible.

*** One participant refused repeat invasive hemodynamic testing but completed all other study procedures.

Figure 3. Pulmonary Capillary Wedge Pressure during Exercise Hemodynamic Testing: Baseline vs. 1 Month Post-Randomization, Stratified by Treatment Group